


February 23, 2001 ET 194217390 US Express Mail

FORM PTO-1390 (REV 5 93)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				HT-109US
				U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
				09/763578
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED		
PCT/US99/18618	23 August 1999 (23.08.99)	24 August 1998 (24.08.98)		
TITLE OF INVENTION METHOD AND DEVICE FOR CONCENTRATING SELECTED GROUPS OF MICROORGANISMS				
APPLICANT(S) FOR DO/EO/US Ruth F. Eden				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(h)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> has been transmitted by the International Bureau. c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 				
Items 11. to 16. below concern other document(s) or information included:				
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.				
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included				
13. <input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.				
14. <input type="checkbox"/> A substitute specification.				
15. <input type="checkbox"/> A change of power of attorney and/or address letter.				
16. <input checked="" type="checkbox"/> Other items or information:				
Small Entity Status is Claimed.				
Better drawing substituted under Article 34 with Demand.				

U.S. APPLICATION NO. (37 CFR 1.53) 09/763578		INTERNATIONAL APPLICATION NO. PCT/US99/18618		ATTORNEY'S DOCKET NUMBER HT-109US	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO..... \$830.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) \$640.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).. \$710.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$950.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... /990/00 \$100 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
				\$ 100.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$ 130.00	
Claims	Number Filed	Number Extra	Rate		
Total Claims	13 -20 =	0	X \$22.00	\$ 0	
Independent Claims	2 -3 =		X \$74.00	\$ 0	
Multiple dependent claims(s) (if applicable)				+ \$230.00	\$ 0
TOTAL OF ABOVE CALCULATIONS =				\$ 230.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$ 115.00	
SUBTOTAL =				\$ 115.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+ \$ 0	
TOTAL NATIONAL FEE =				\$ 115.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
TOTAL FEES ENCLOSED =				\$ 115.00	
				Amount to be:	
				refunded \$	
				charged \$	
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>115.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. _____. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: James M. Deimen 320 N. Main Street, Suite 300 Ann Arbor, Michigan 48104-1192					
				 SIGNATURE James M. Deimen	
				NAME _____	
				25504 _____	
				REGISTRATION NUMBER	

**Method and Device for Concentrating Selected Groups
of Microorganisms**

5 Background -- Field of Invention.

This application is based on provisional patent application Serial No. 60/097,627, filed August 24, 1998.

The present invention relates to products and processes used for the detection of microbes in a sample. More specifically, the present invention provides a method and device for aiding in the detection of the presence of specific microbial contamination in food samples, clinical specimens and other products.

Background -- Prior Art.

It is necessary to test various substances, such as foods, beverages, pharmaceuticals, cosmetics, water, and body fluids for microbial contamination, especially with certain pathogenic bacteria. Recent outbreaks of foodborne illness, implicating a variety of foods contaminated with pathogenic bacteria, such as *E. coli* 0157:H7, *Salmonella*, *Listeria*, *Campylobacter jejuni*, and *Cyclospora*, have underscored the need for rapid methods for microbiological analysis. Microbiological analysis is critical for assessment of safety and quality, to determine efficiency of manufacturing, and conformance with regulations.

The increased scope, significance, and need for microbiological testing served to reveal the limitations and drawbacks of conventional methods. Classical methods for determining the presence of pathogenic bacteria in samples are taking typically several days to perform. It is desired to provide rapid detection of especially pathogenic bacteria causing illnesses.

Since the desired sensitivity for most assays for pathogenic bacteria is less than one such organism in 25 grams of product, most testing methods rely on an initial enrichment step. The indigenous microflora that is usually present in many foods at high levels often interferes with the selective isolation and identification of pathogenic bacteria. Food processing such as heating, cooling, drying,

freezing, addition of preservatives and other causes can sub-lethally injure bacterial cells. These injured cells are extremely sensitive to the ingredients used in selective microbiological media. Therefore, in many assays the process starts with pre-enrichment, in which the sample is incubated in a nutritious, non-selective medium to allow the resuscitation of injured or stressed bacteria. This step is followed by a selective enrichment step where the bacteria of interest are allowed to grow while the indigenous microflora is suppressed. The enrichment procedure is followed either by conventional plating methodology or a variety of more modern and rapid methods such as DNA amplification or immunoassay.

It is therefore desired to separate at an early stage the target organisms from the other flora present in the product. One such approach is the utilization of the immuno-magnetic separation technique, involving the utilization of immuno-magnetic particles specific for the target organisms. Magnetic beads with antibodies affixed to their surfaces are mixed with the sample containing the target organism. This organism will bind to the bead surfaces via the antibodies. The organism-bead complex is pulled out of the solution by a magnet, to concentrate the microorganisms.

U.S. patent 4,230,685 describes magnetically responsive microspheres having protein A associated with the outer surface. The microspheres are reacted with antibodies selective to cells, bacteria or viruses to be separated from a mixed population. The microorganism will attach to the antibody and thereby to the microspheres, and the microspheres are then used in a magnetic separation procedure. The preferred microspheres are prepared from a mixture of albumin, Protein A, and magnetic particles. The microspheres are prepared so that the Protein A is present in the exterior surface of the antibody binding. U.S. patent 4,695,393 describes a process for the preparation of such magnetic beads, which can be used in separation of microorganisms.

U.S. patents 5,491,068 and 5,695,946 describe a method characterized by antibody capture of the organism of interest by the application of specialized magnetic beads. It entails the incubation of the capture cells to form colonies; removal of material from the colonies with colony lift membrane; and detection of the colony material on the membrane sheet by the use of labeled antibodies, PCR or nucleic acid probes. The main problem with this method is the low

sensitivity of one organism per gram. This low sensitivity is inherent in the methodology and is 50-100 fold lower than the desired sensitivity for most food pathogens.

U.S. patent 4,677,055 describes a process for concentrating bacteria
5 utilizing magnetic gel to which anti-specific antigenic determinant antibodies are coupled. It involves the steps of obtaining medium containing the organisms possessing specific antigenic determinants and bringing them in contact with particles of the magnetic gel. This step is followed by the separation of the gel from the medium by magnetic means and inoculation into new medium.

10 In general there are a number of problems associated with magnetic beads. One such problem results from the small size of such beads (3-10 μm) and the large volume of the medium (250-3,000 ml). As a result it is impossible to remove the magnetic beads from such a large volume. Therefore, many procedures either use a lower sample volume (thereby reducing the sensitivity of
15 the assay) or allow some time (8-18 hours) of pre-enrichment followed by the removal of 1-5 ml of solution for concentration of the target organisms. Another problem associated with the magnetic beads is the fact that they get coated with fat and proteins making it difficult to be collected with a magnet. The process of separating the beads from the medium and washing the unattached bacteria is
20 labor intensive, and creates a contamination hazard of both laboratory surfaces and the beads.

Objects and Advantages.

It is, therefore, an object of the invention to provide a method and device that can be utilized with a large volume of media, to concentrate a target
25 organism. It is another object of the invention to provide a method that is less labor intensive, more rapid and will lend itself to automation.

Still further objects and advantages will become apparent from a consideration of the ensuing description and accompanying drawings.

Brief Description of the Drawings.

30 Fig. 1 shows a side view of the preferred device utilized to concentrate target organisms.

Fig. 2 shows a side view of another design of the device utilized to concentrate target organisms.

Preferred Embodiment -- Description.

Figure 1 shows the preferred embodiment of a device for the separation of the target organisms from a suspension containing a mixture of organisms. Beads 1 are made of materials such as nylon, polystyrene or glass. The beads are coated with antibodies to specific microorganisms such as *Salmonella*, *E. coli* 0157:H7 and *Listeria*. A cylindrical enclosure 2 is designed to contain the beads. The enclosure is constructed from a frame 3 supporting a grid 4 covering the frame. The grid's pore size is smaller than the size of the beads to assure that the beads stay within the enclosure 2. However, the pore size is large enough to allow bacteria to freely pass into the enclosure. A rod 5 is attached to the upper part of the enclosure. The rod 5 allows the enclosure 2 to move in the solution and for subsequent removal of the device from the solution.

Figure 2 shows a different design of the device. The beads 11 coated with antibodies are contained in the enclosure 12 made of a grid 13, shaped like a tea bag. A non-wicking string 14 is attached to the upper part of the enclosure 12 allowing movement of the enclosure 12 in the solution, while disallowing the solution containing bacteria to wick up the string. The grid's 13 pore size is smaller than the size of the beads to assure that the beads stay within the enclosure. However, the pore size is large enough to allow bacteria to freely pass into the enclosure.

The food sample to be tested for the presence of the target organism is mixed with the appropriate pre-enrichment broth. The pre-enrichment broth is incubated at an appropriate temperature. Upon the beginning of the incubation period, or alternatively after several hours of incubation, the enclosure 2 is immersed into the broth containing the sample thereby exposing the beads having immobilized thereon monoclonal or polyclonal antibodies to the selected bacteria of interest. This is accomplished by lowering the device 2 into the solution and agitating it for at least 30 minutes and up to several hours. This step allows cell capture by the beads, and the creation of bead-target microbial cell complexes. The next step involves the separation of the beads with the bound target cells from

the suspension containing the food particles and other mixed flora. This is accomplished by pulling the whole device out of the solution, using the rod 5. The device is subsequently washed several times in sterile saline or buffer solution. The washing solution is changed after each wash to remove non-bound organisms. Addition of detergents such as Tween-20 (0.51-0.1 % w/v) or protamine to the incubation broth mixture usually decreases the non-specific adsorption. Tween-20 can be also used in the washing procedure to remove non-specifically bound cells. After the wash step a number of methods can be utilized to detect the presence of the target organism.

Several detection procedures can be used in conjunction with the current invention to detect the presence of the microorganism of interest. For example, the device can be inserted into a new growth broth that includes a dye indicator and the changes in the dye characteristics can be utilized to determine presence or absence of the target organism. The microorganisms do not need to be detached from the beads since attachment to the beads has no effect on their growth. Therefore cells can continue to multiply in the appropriate medium. Alternatively the beads can be removed from the enclosure and inoculated onto the surface of appropriate selective or differential agar. Another approach is to utilize an immunoassay. Most immunoassays require 10^3 - 10^5 cells ml^{-1} , therefore the beads should contain enough cells to perform a direct immunoassay. Similarly, this method can be combined with DNA hybridization and amplification techniques such as PCR.

As can be seen from the above disclosure, the method of the invention is particularly characterized by the use of immunological beads contained in an enclosure to select out target microorganisms from the sample. The beads must be capable of effectively capturing the target microorganisms from the test sample, while not capturing significant numbers of other organisms that might be present at much higher numbers. However, the antibody used need not be totally specific to the target organism since an additional selection step is available at the end of the assay. The antibodies must be oriented with their binding sites outward to allow contact between the binding portion of the antibody and the target organism. The size of the beads must be larger than the size of the microorganism, to remain contained in the enclosure, while allowing the target

organism to enter the enclosure and attach to the beads. The contact time between the beads and the target organism must be long enough to allow strong interaction. Several hours of interaction was found to yield the best results, i.e. the creation of strong interactions to produce high capture efficiency. After the completion of the incubation step the beads are removed from the solution, by the removal of the enclosure in which they are contained. The enclosure and the beads are washed several times, and the beads are transferred into the detection system.

Conclusions, Ramifications, and Scope.

Accordingly, it can be seen that the new method and device can be utilized with a large volume of media, to concentrate a target organism, without the need to utilize only a portion of the pre-enrichment broth or a small volume of enrichment broth as required for magnetic beads. The invention provides a method and device that is less labor intensive, more rapid and lends itself to automation. Many different designs, for containing the beads during the various steps of the assay, can be utilized.

Obviously, many modifications and variations of the present invention are possible in light of the above techniques. Although the description above contains many specificities, these should not be construed as limiting the scope of the invention but as merely providing illustrations of some of the presently preferred embodiments of this invention. The invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A device for separating specific target microorganisms from suspension containing mixed groups of microorganisms, comprising:
a plurality of beads coated with at least one antibody material to
5 capture the target microorganisms; and
an enclosure made of a grid material enclosing said beads, with a pore size smaller than the size of said beads and larger than the size of the microorganisms.
2. The device of claim 1 wherein said beads are made of resinous
10 material.
3. The device of claim 1 wherein said beads are made of non resinous material.
4. The device of claim 1 further comprising means to agitate said enclosure in the suspension.
- 15 5. A method of separating target microorganisms from a suspension containing mixed groups of microorganisms, comprising:
immersing a plurality of beads coated with at least one antibody material into the suspension, said beads being held by an enclosure made of a grid with a pore size smaller than the size of said beads and larger than the size of the
20 microorganisms, thereby allowing the capture of the target microorganisms by said beads; and
washing said beads to remove organisms not bounded to said beads, after pulling said enclosure from the suspension.
6. The method of claim 5 wherein at least one detergent is applied in
25 said washing.
7. The method of claim 5 further comprising agitation of said enclosure holding said beads in the suspension.

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8. The method of claim 7 wherein the time period of agitation is at least 30 minutes.

5 9. The method of claim 7 wherein the time period of agitation extends for several hours.

10 10. The method of claim 5 including the addition of at least one detergent to the suspension to decrease adsorption of non-specifically bound cells.

11. The method of claim 5 including the subsequent step of immersing the enclosure and beads in a new growth broth.

12. The method of claim 11 including the addition of an indicator material to the new growth broth.

13. The method of claim 5 including the subsequent step of separating the beads from the enclosure followed by at least one test to reveal the microorganisms of interest.

15 (JMD\Eden - p.7a to Pat. Applic.)

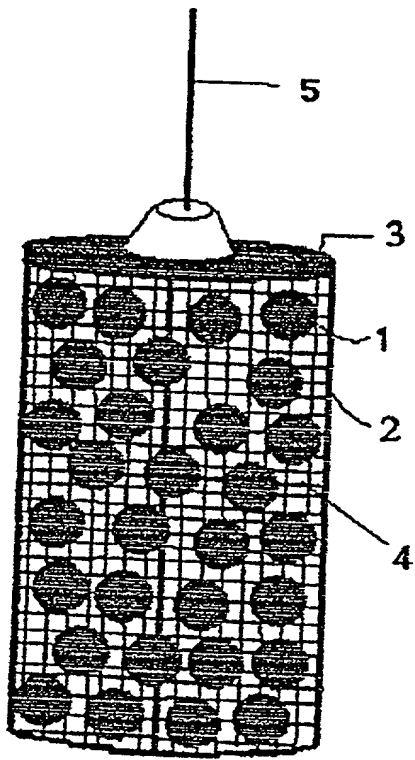


Fig. 1

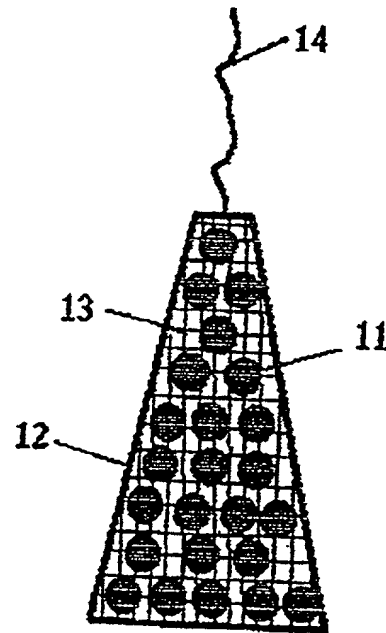


Fig. 2

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	HT-109US
	First Named Inventor	Ruth F. Eden
	COMPLETE IF KNOWN	
	Application Number	09 / 763,578
	Filing Date	02/23/01
	Group Art Unit	
<input type="checkbox"/> Declaration Submitted with Initial Filing	OR	<input checked="" type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)
	Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD AND DEVICE FOR CONCENTRATING SELECTED GROUPS OF MICROORGANISMS

the specification of which

(Title of the Invention)

☐ is attached hereto
OR

☒ was filed on (MM/DD/YYYY) 02/23/01

as United States Application Number or PCT International

Application Number 09/763,578 and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.
60/097,627	08/24/98	

[Page 1 of 2]

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(e) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/US99/18618	08/23/99	

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As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number

OR

☒ Registered practitioner(s) name/registration number listed below

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Name	Registration Number	Name	Registration Number
James M. Deimen	25504		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

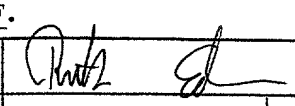
Direct all correspondence to: ☐ Customer Number OR ☒ Correspondence address below

Name	James M. Deimen				
Address	320 N. Main Street, Suite 300				
Address					
City	Ann Arbor	State	MI	ZIP	48104-1192
Country	USA	Telephone	734-994-5947	Fax	734-769-2702

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

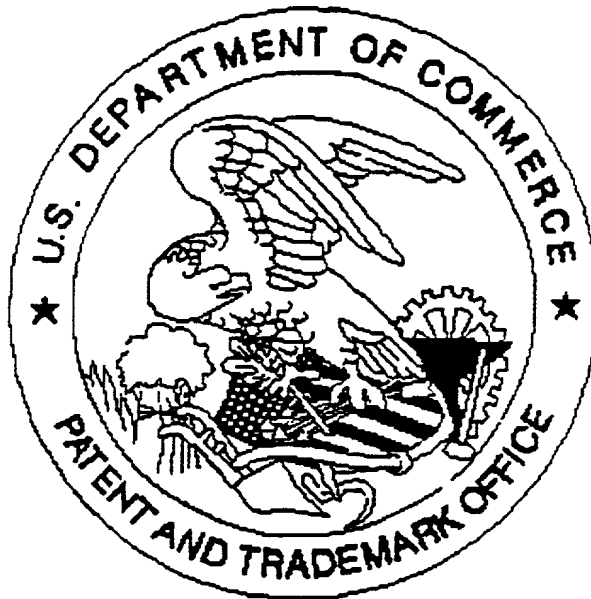
Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))		Family Name or Surname					
Ruth F.		Eden					
Inventor's Signature				Date	06/06/00		
Residence: City	Ann Arbor	State	MI	Country	USA	Citizenship	USA
Post Office Address	2765 Ember Way						
Post Office Address							
City	Ann Arbor	State	MI	ZIP	48104	Country	USA

☐ Additional inventors are being named on the _____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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Application deficiencies found during scanning:

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